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Comparison of Dexmedetomidine and Midazolam for sedation in Mechanically ventilated patients in Neurology ICU setup

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ABSTRACT

Introduction: The main interest of the current article was to determine and investigate the effects of Dexmedetomidine in comparison to Midazolam required for sedation of the patients on Mechanical ventilation in Neurology ICU as sedative agents using RASS (Richmond Agitation sedation scale) to assess sedation level. The time required for the extubation of the patients after stopping two sedatives was compared between the two groups. *Material and methods:* This was a randomized, prospective, and comparative study conducted on the patients of ASA classes II and III who were on mechanical ventilators requiring sedation in Neurology ICU from the period October 2021 to April 2022 at the Department of Anaesthesia, Jawaharlal Nehru Medical College, Acharya Vinoba Bhave rural hospital (AVBRH), Sawangi, Meghe. All the patients were more than 18 years and less than 70 years old. *Results:* The time to achieve the target sedation range was statistically significant. In group A, the patient's time taken was 10.36 minutes as compared to 7.43 minutes in group B. The difference between the two groups concerning the time required for extubation was statistically significant. The time needed for extubating the patient after stopping Midazolam was more than the Dexmedetomidine group. *Conclusion:* In comparing two sedative drugs, it was found that Dexmedetomidine as a sedative resulted in early weaning from the mechanical ventilator compared to Midazolam in ICU Patients. However, Dexmedetomidine was found to have more occurrences of hypotension and bradycardia as compared to Midazolam.

Keywords: Sedation, Intensive care unit, Dexmedetomidine, Midazolam, mechanical ventilation, Glasgow coma scale.

1. INTRODUCTION

In Intensive Care Unit (ICU), patients are usually in need of many uncomfortable and invasive procedures and interventions such as prolonged ventilator support requiring endotracheal intubation, central venous catheterization, Ryle's tube insertion, and many more. Sedation is frequently used to lessen patients' anxiety, improve tolerance, and enhance the results of such therapies (Mehta et al., 2011). G-amino butyric receptor agonists, such as benzodiazepines like Midazolam and Propofol, are used as sedatives in the ICU (Aitken et al., 2015). Achieving the right level of sedation is crucial for balancing between relieving pain and keeping patients tranquil and avoiding oversedation and lengthening ICU Stays (Hynes-Gay et al., 2003). Sedation breaks can be recommended to gauge sedation levels, assess the GCS of neurologically impaired patients, and prevent oversedation and related adverse effects.

Thus, optimizing sedation and analgesia for patients requiring mechanical ventilation support is mandatory. Many methods are used to assess ICU. Patients' sedation level. Objective methods like Bispectral Index and EEG – Electroencephalogram Fuchs and Rueden, (2008) and subjective methods like sedation scores which include Richmond agitation - sedation scale (RASS), Ramsay sedation scale and Riker sedation agitation scale (SAS) (Mirski et al., 2010). The two sedative medications, Dexmedetomidine and Midazolam, were used in the current study, and their effectiveness was compared. This article's main aim was to compare and determine the amount of time needed for extubation after the two sedative agents were stopped. The secondary goal of the study was to compare the two drugs' safety and effectiveness by noting hemodynamic measures like heart rate and noninvasive blood pressure.

Dexmedetomidine is a concrete and selective presynaptic alpha 2 agonist with additional analgesia properties, anxiolysis, and sympatholytic effects apart from sedation. Activating spinal cord and brain receptors that stop neuronal firing causes sedation, analgesia, hypotension, and bradycardia. In addition to possessing analgesic qualities, Dexmedetomidine outperforms commonly used ICU. Sedatives like Midazolam and Propofol, helps reduce the demand for opioids and the adverse effects that come along with them (Myatra, 2014). Dexmedetomidine has the added advantage of providing sedation without causing respiratory depression. A benzodiazepine drug, Midazolam is another sedative agent which is used for the prevention of delirium and agitation in ICU patients. Like Dexmedetomidine, midazolam has no analgesic and sympatholytic properties. In the Neurology ICU the Richmond Agitation-Sedation Scale was used to determine the efficacy and safety of Dexmedetomidine and midazolam as a subjective method in managing sedation for patients on mechanical ventilators.

Aims and objective

The aim of this article was to assess the safety and the effectiveness of Dexmedetomidine in comparison to Midazolam required for the sedation of the patients on mechanical ventilator support in neurology ICU setup.

The primary objective was to compare the time required for extubation of the patients after stopping the sedative agents.

The secondary objective was to determine the safety and effectiveness of the two sedatives in comparing hemodynamic vitals like heart rate and noninvasive blood pressure.

2. METHODS

This was a randomized, prospective, and comparative study conducted on the patients who were on mechanical ventilators requiring sedation in the intensive care unit of neurology from the period October 2021 to April 2022, in the Department of Anaesthesia, Jawaharlal Nehru Medical College, Acharya Vinoba Bhave rural hospital (AVBRH), Sawangi, Meghe. Informed and written consent was obtained from all the participants and their relatives in the study.

Inclusion Criteria

ASA class II and III patients of either gender with age more than 18 years and less than 70 years requiring mechanical ventilation support were involved in the study.

Exclusion Criteria

1. Patients with known allergy to Dexmedetomidine and Midazolam.
2. Patients with severe hepatic derangement and renal insufficiency requiring dialysis.
3. Those patients who were transferred from outside institution.
4. Those patients who were admitted after resuscitation from heart failure.
5. Patients on neuromuscular blockade agents.

Sixty patients were enrolled for the study, with 30 patients in each group.

Group A: Dexmedetomidine was used as a sedative.

Group B: Midazolam was used as a sedative.

Group A patients received intravenous infusion of injection Dexmedetomidine with a bolus dose of 1 micrograms/kilogram over 10 minutes, followed by infusion at a rate of 0.2 – 0.7 micrograms/kilograms /hour.

Group B patients received an intravenous infusion of injection Midazolam as an initial loading dose of 0.5 to 5 milligrams every 1 to 5 minutes as needed. Continuous infusion at 1- 2 milligrams/hour, with the increase in the dose until sufficient sedation was obtained, as with intravenous injection of Dexmedetomidine.

Agitation was monitored for a minimum of 3 days of sedation. Drugs were titrated to maintain target sedation RASS score -2 to-3 (Table 1).

After stopping infusions of sedatives in the two groups, the time to extubation was recorded. Data was collected until the patients were extubated.

Table 1 Richmond Agitation Sedation Score.

Score	Term	Description
+4	Combative	Violent, Immediate Danger to Staff
+3	Very Agitated	Pulls Catheters, Tubes (Aggressive)
+2	Agitated	Aimless movement, fights Ventilator
+	Restless	Anxious but Movements not Aggressive
0	Alert and Calm	-
-1	Drowsy	Not fully alert but has eye contact and opening >10 s
-2	Light Sedation	Briefly Awakens with eye Contact <10 s
-3	Moderate Sedation	Movement or eye opening to voice with no eye Contact
-4	Deep Sedation	No response to voice, responds to physical stimulation by movement or eye opening
-5	Unarousable	No response to voice or Physical Stimulation

Statistical Analysis

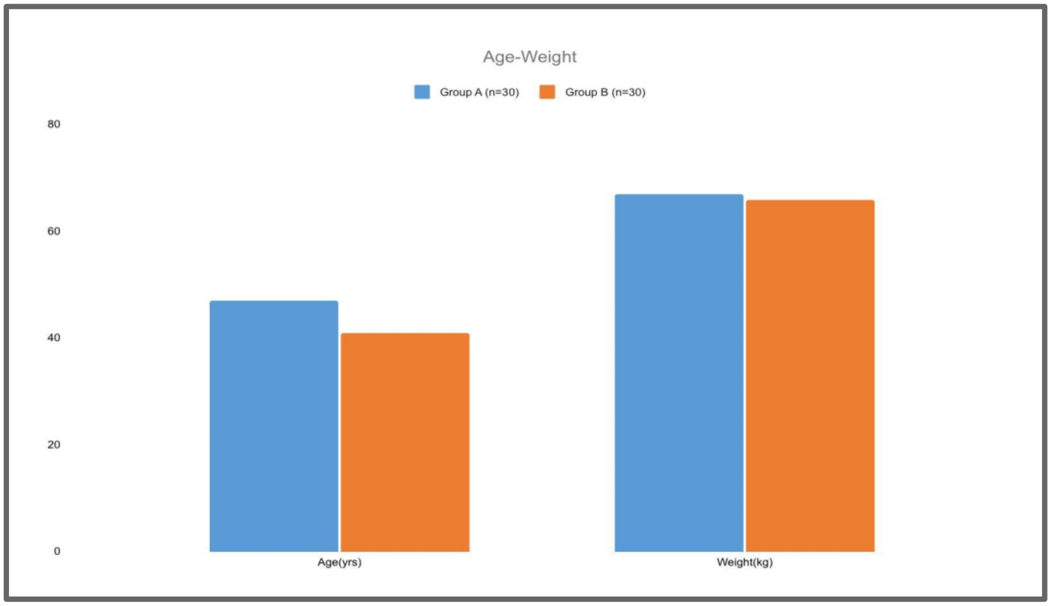
The data was statistically analyzed using SPSS 25.0. Information was presented as mean +/- S.D. For comparisons of repeated measures within groups, the paired sample t-test was applied, while the independent sample t-test was employed for comparisons between groups. The X2 test was used to examine the nonparametric data. Statistics were deemed significant at P 0.05. A minimum of 28 patients in individual groups were needed to detect a mean difference of 1 for RASS scores between the two groups using an alpha level of 0.05 and a power of 0.80.

3. RESULTS

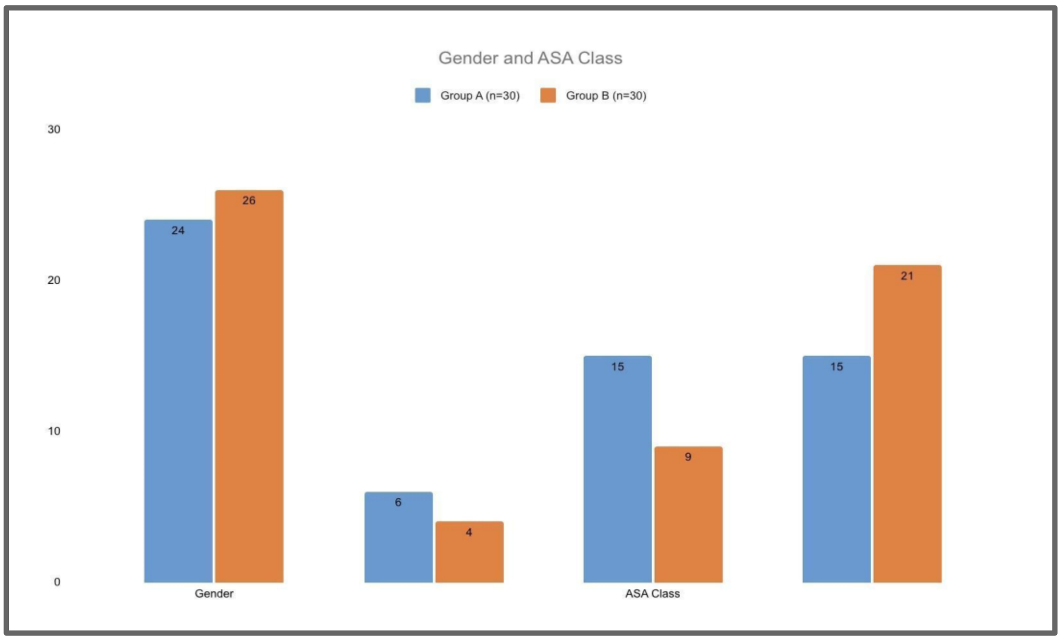
Table 2 Showing Patients profiles in view of age in years, weight in kilograms, gender and ASA class. The difference among the two groups was statistically not significant with respect to age and weight, gender and ASA grade (P value > 0.05) (Graph 1 and 2).

Table 2 Patients Profile

Variable		Group A (n=30)		Group B (n=30)		t-Value	χ2-Value
		Mean	S.D.	Mean	S.D.		
Age (yrs)		46.86	12.18	40.86	15.12	1.69	0.096, NS
Weight (kg)		66.93	2.33	65.83	2.19	1.87	0.096, NS
Gender	Male	24	80%	26	86.67%	-	X2 = 0.48 p = 0.48 NS
	Female	6	20%	4	13.33%	-	
ASA Class	Class II	15	50%	9	42.85%	-	X2 = 2.50 0.11, NS
	Class III	15	50%	21	57.15%	-	



Graph1 Patients profile in view of Age (years) and weight (kilograms).



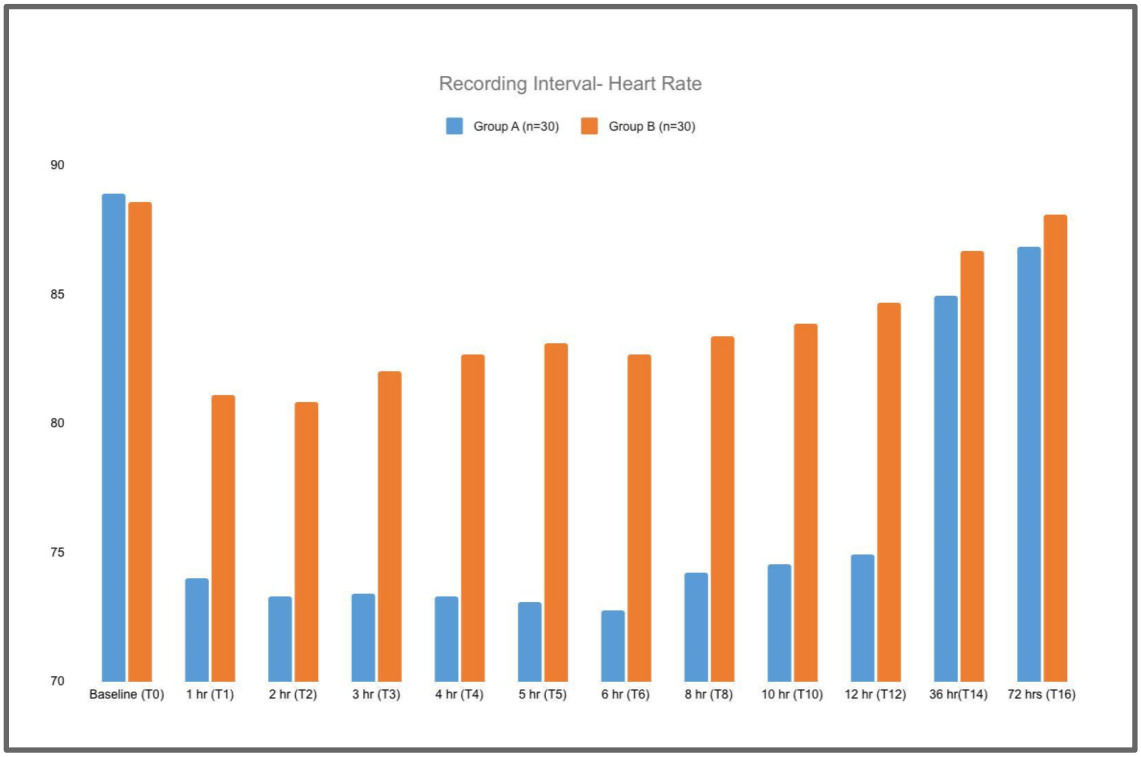
Graph 2 Patients profile in view of Gender and ASA class.

Table 3 Comparing Hemodynamic parameter of Heart rate between two groups in per minute. In group A patients there was statistically significant decrease in mean HR from the baseline from 1st hour after the initiation of sedative dexmedetomidine till 12 hrs (P value= 0.0001). Bradycardia was noted as one of the side effects in group A patients who received Dexmedetomidine as compared to the patients who were sedated with midazolam (Graph 3).

Table 3 Heart Rate

Recording Interval	Group A (n=30)			Group B (n=30)			t-Value	p-Value
	Mean	S.D.	% Change	Mean	S.D.	% Change		
Baseline (T0)	88.87	6.12	-	88.53	5.30	-	0.22	=0.82 NS
1 hr (T1)	74.00	4.23	16.73	81.07	4.16	8.43	6.52	=0.0001 S
2 hr (T2)	73.27	5.57	17.55	80.80	3.99	8.73	6.02	=0.0001 S
3 hr (T3)	73.40	4.40	17.41	82.00	3.19	7.38	8.66	=0.0001 S
4 hr (T4)	73.27	4.88	17.55	82.67	3.42	6.62	8.63	=0.0001 S

5 hr (T5)	73.07	5.67	17.78	83.07	4.95	6.17	7.27	=0.0001 S
6 hr (T6)	72.73	6.20	18.16	82.67	5.49	6.62	6.56	=0.0001 S
8 hr (T8)	74.20	5.69	1.65	83.33	3.94	0.75	7.22	=0.0001 S
10 hr (T10)	74.53	5.96	16.14	83.87	3.71	5.26	7.27	=0.0001 S
12 hr (T12)	74.93	5.03	15.69	84.67	3.61	4.36	8.60	=0.0001 S
36 hr (T14)	84.93	4.19	4.43	86.67	3.38	2.10	1.76	= 0.08 NS
72 hrs (T16)	86.80	4.35	2.33	88.07	3.26	0.52	1.27	=0.20 NS



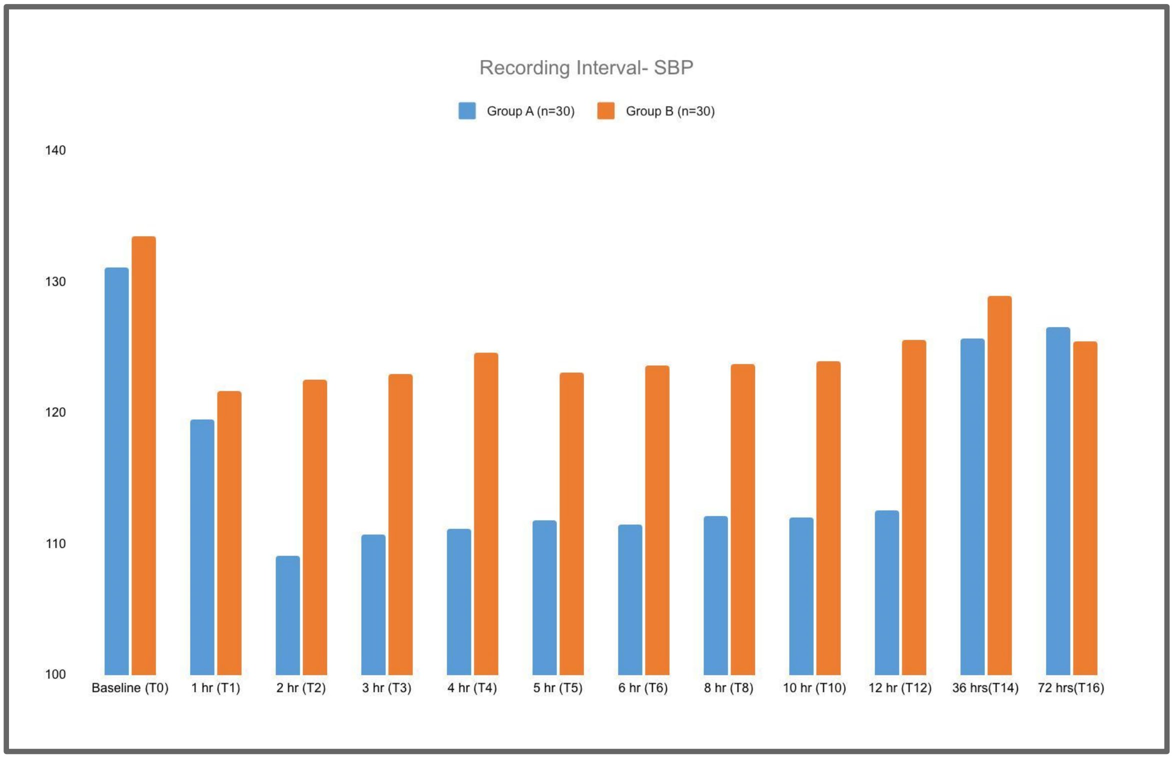
Graph 3 Comparing Hemodynamic parameter of heart rate between two groups after starting sedation from the baseline heart rate.

Table 4 Systolic blood pressure

SBP	Group A (n=30)			Group B (n=30)			t-Value	p-Value
	Mean	S.D.	% Change	Mean	S.D.	% Change		
Baseline (T0)	131.00	6.88		133.47	4.58		1.63	0.108 NS
1 hr (T1)	119.40	8.50	8.85	121.67	5.23	8.84	1.24	=0.2188 NS
2 hr (T2)	109.00	7.71	16.79	122.53	4.64	8.20	9.23	=0.0001 S
3 hr (T3)	110.67	6.09	15.52	122.87	4.45	7.94	8.86	=0.0001 S
4 hr (T4)	111.07	6.05	15.21	124.53	5.61	6.70	8.94	=0.0001 S
5 hr (T5)	111.80	6.38	14.66	123.00	5.60	7.84	7.22	=0.0001 S
6 hr (T6)	111.47	6.52	14.91	123.60	4.94	7.39	8.12	=0.0001 S
8 hr (T8)	112.13	6.26	0.50	123.67	5.59	0.05	7.53	=0.0001 S
10 hr (T10)	112.00	6.26	14.50	123.93	4.35	7.15	8.57	=0.0001 S
12 hr (T12)	112.53	6.24	14.10	125.53	6.55	5.95	7.87	=0.0001 S
36 hrs (T14)	125.67	7.34	4.07	128.93	4.63	3.40	2.02	=0.044 S
72 hrs (T16)	126.53	6.21	3.41	125.40	4.21	6.05	0.82	= 0.41 NS

Table 4 Comparing hemodynamic parameter of Systolic Blood Pressure between two groups in millimetres of mercury. There was decrease in systolic blood pressure in millimetres of mercury from the baseline from first hour after starting dexmedetomidine

sedation till 36 hours (P value = 0.0001). Hypotension was noted as one of the side effects in group A patients who received Dexmedetomidine as sedative as compared to the patients who were sedated with midazolam in group B (Graph 4).

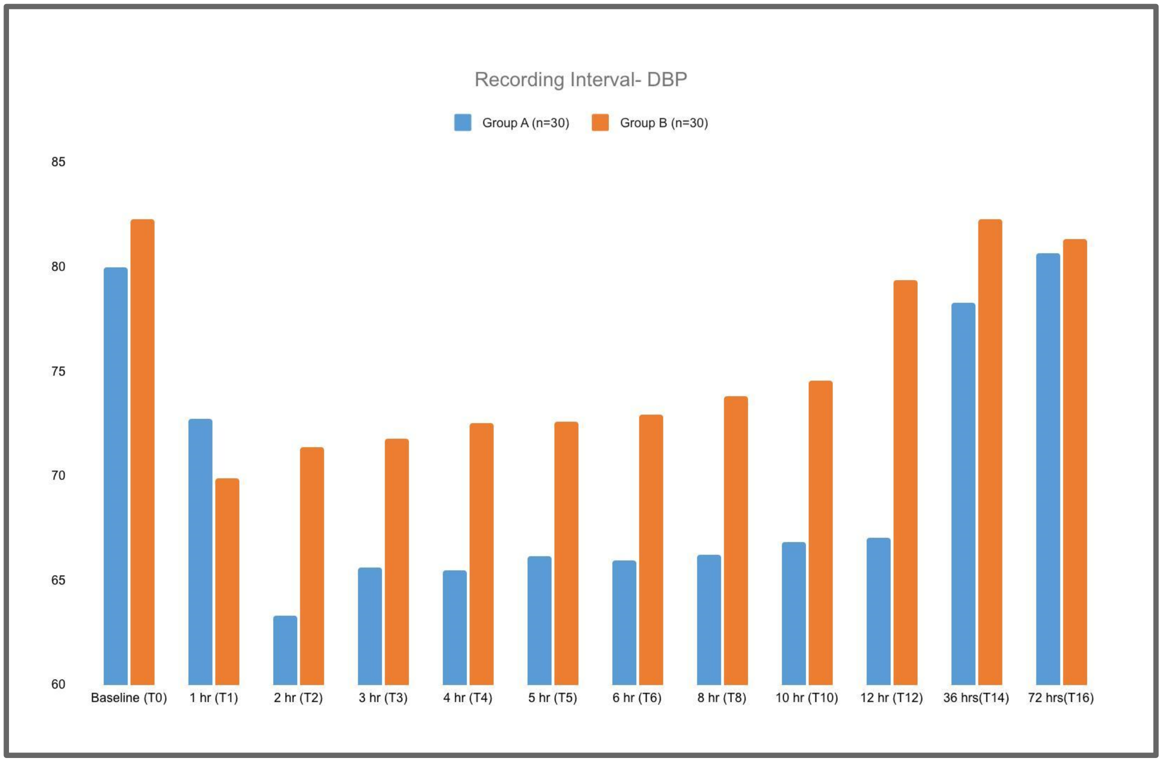


Graph 4 Comparing Hemodynamic parameter of systolic blood pressure between two groups after starting sedation from the baseline systolic blood pressure.

Table 5 Diastolic blood pressure

Recording Interval	Group A (n=30)			Group B (n=30)			t-Value	p-Value
	Mean	S.D.	% Change	Mean	S.D.	% Change		
Baseline (T0)	79.93	4.31	-	82.27	4.95	-	1.94	= 0.0566 NS
1 hr (T1)	72.73	4.38	9.01	69.87	4.23	15.07	2.57	= 0.0124 S
2 hr (T2)	63.27	3.62	20.84	71.33	3.61	13.30	8.63	=0.0001 S
3 hr (T3)	65.60	2.75	17.93	71.73	3.31	12.81	7.80	=0.0001 S
4 hr (T4)	65.47	2.57	18.09	72.47	3.74	11.91	8.45	=0.0001 S
5 hr (T5)	66.13	2.22	17.27	72.53	3.10	11.84	9.17	=0.0001 S
6 hr (T6)	65.93	2.13	17.52	72.87	2.66	11.43	11.13	=0.0001 S
8 hr (T8)	66.20	2.19	0.34	73.80	2.31	1.13	13.08	=0.0001 S
10 hr (T10)	66.80	2.66	16.43	74.53	2.16	9.41	12.36	=0.0001 S
12 hr (T12)	67.00	2.51	16.18	79.33	4.21	3.57	13.78	=0.0001 S
36 hrs (T14)	78.27	4.63	2.08	82.27	4.19	0.00	3.50	=0.001 S
72 hrs (T16)	80.60	2.58	0.84	81.33	3.73	1.14	0.88	= 0.37, NS

Table 5 Comparing Hemodynamic parameter of Diastolic blood pressure between two groups in millimetres of mercury. There was decrease in diastolic blood pressure in millimetres of mercury from the baseline from first hour after starting dexmedetomidine sedation till 36 hours. (P value 0.0001). Hypotension was noted as one of the side effects in group A patients who were sedated with Dexmedetomidine as compared to the patients who received midazolam (Graph 5).

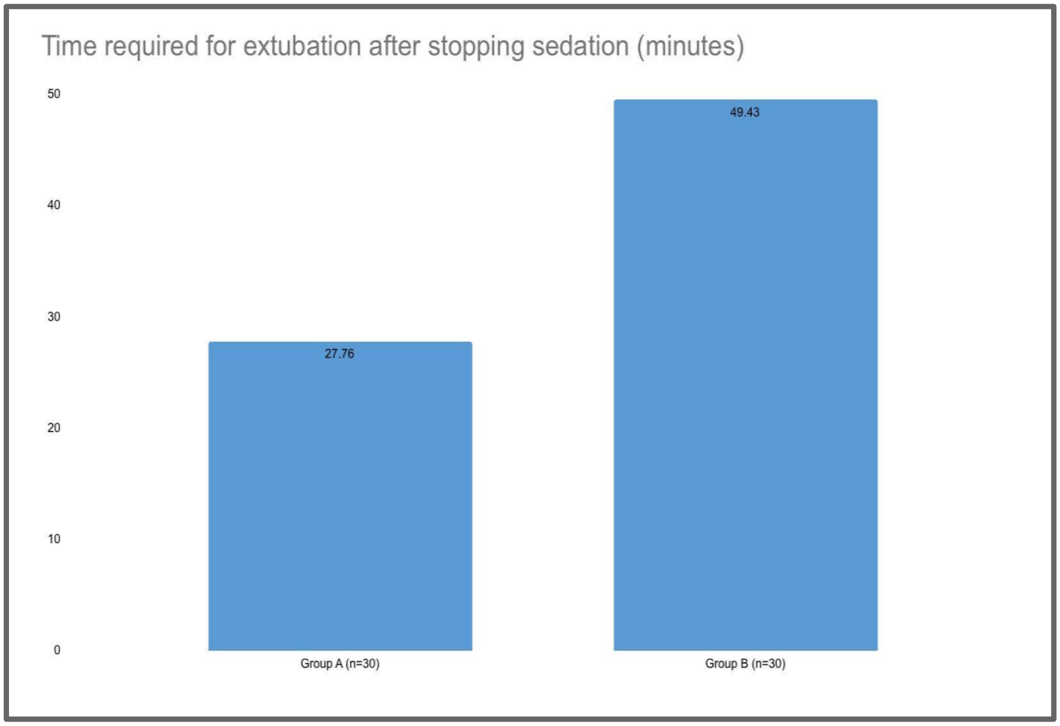


Graph 5 Comparing Hemodynamic parameter of Diastolic blood pressure between two groups in millimetres of mercury after starting sedation from the baseline diastolic blood pressure.

Table 6 Time required for Extubation (After stopping of Sedation)

Variable	Group A (n=30)		Group B (n=30)		t-Value	P-Value
	Mean	S.D.	Mean	S.D.		
Time required for Extubation (after stopping Sedation) (Minutes)	27.76	11.74	49.43	5.58	9.12	0.00001, S

Table 6 compares the time required for extubating the patient in minutes after stopping sedation in between two groups. The time needed for extubation after stopping sedation was more in group B patients as compared to group A patients who received Dexmedetomidine. Patients receiving dexmedetomidine were weaned early from mechanical ventilators as compared to patients who received midazolam (27.6 minutes in Group A as compared to 49.43 minutes in group B). Group B patients spent more time on mechanical ventilators than group A patients who were sedated with Dexmedetomidine (Graph 6).



Graph 6 Time required for extubation after stopping sedation in minutes.

4. DISCUSSION

For almost every patient in the critical care unit, sedation is provided for comfort and is an essential concept of bedside treatment. The most frequently prescribed sedative medications for ICU patients globally have been gamma-aminobutyric acid (GABA) receptor agonists like Propofol and benzodiazepines like Midazolam for many years. Few studies on sedation required in ICU have compared GABA agonists to other medications, despite the well-known risks linked to their chronic use. Our study's primary objective was to note the required time for extubation after stopping infusions of two sedative agents, Dexmedetomidine and Midazolam, in neurology ICU setup (Riker et al., 2009).

Anxiety, pain, endotracheal intubation, and the presence of monitoring devices are among the factors that cause discomfort to patients in critical care units. Patients admitted in Intensive care units are very prone to delirium and therefore require good sedation. The best way to relieve their agony is by providing them with intravenous sedatives and opioids. Sedation has consequently grown to be a crucial component of critical care practice. Sedation mainly helps to ease anxiety, improves the patient's tolerance capacity for being on ventilator support, and improves required nursing care (Mazzeo, 1995; Tung and Rosenthal, 1995).

The ideal sedative should have the following characteristics:

1. Quick action,
2. Quick recovery after withdrawal.
3. Ease of administration.
4. Fewer adverse effects.
5. Minimal drug interactions and cost effectiveness (Ostermann et al., 2000).

There are multiple routes by which sedatives can be administered, such as oral, inhalational, and intramuscular. However, the intravenous route is the most preferred one as the dose can be easily titrated according to the response of the patient and the fast onset of action. Multiple groups of drugs are used as sedative agents, such as benzodiazepines, namely Midazolam and lorazepam, centrally acting alpha 2 agonists like Dexmedetomidine, clonidine, opioids like fentanyl and Propofol which acts on GABA receptor. Midazolam is a benzodiazepine, which acts via the GABA receptor, which has a rapid rate of elimination, high lipophilicity, and fast rate of elimination, resulting in shorter duration of action (Smyth and Stead, 2002; Pickles et al., 2003; Stolz et al., 2004).

However, dose-dependent prolonged sedation, cognitive changes, and respiratory depression may occur in older adults and those with hepato-renal dysfunction (Olkkola and Ahonen, 2008; Clark et al., 2009). The dose of Midazolam for ICU sedation consists of a bolus dose of 0.05mg/kg over 10 minutes, followed by a maintenance dose of 0.1mg/kg/hr. Dexmedetomidine is an alpha 2 adrenoreceptor agonist which acts centrally, attenuates the stress response without causing respiratory depression, and causes drowsiness by activating receptors in the spinal cord and locus coeruleus. Dexmedetomidine has various effects, including hypnosis, analgesia, anesthesia, and anxiolysis (Kemp et al., 2008). It can encourage cooperative sedation. Dexmedetomidine's main benefit is that it can be administered till the end and even at the time of extubation without the risk of respiratory depression. (Sessler and Varney, 2008; Gomez-Vazquez et al., 2007).

Dexmedetomidine has a short distribution half-life (about 6 minutes), which sedates the patients quickly, and has a short elimination half-life (approximately 2 hours) that, speeds up drug clearance (Lam and Alexander, 2008). The required dose for sedation in ICU is a bolus dose of 1ug/kg over 10 minutes followed by continuous infusion of 0.2-0.7ug/kg/hr—higher doses of dexmedetomidine result in significant hypotension and bradycardia. For the patients dependent on mechanical ventilation. Riker et al., (2009) studied the safety and efficacy of extended sedation with Midazolam versus Dexmedetomidine. From putting them on ventilators after intubation till their extubation, dexmedetomidine 0.2 - 1.4 mcg/kg/hr or midazolam 0.02 -0.1 mg/kg/hr was titrated to gain light sedation (RASS score between -2 and +1).

No difference was noted between the Dexmedetomidine group's 77.3% and the Midazolam group's 75.1% time spent within the desired RASS range. The median time till extubation was 1.9 days shorter in individuals receiving Dexmedetomidine (Riker et al., 2009). They thus concluded that at corresponding levels of sedation, those patients who received Dexmedetomidine had less time on mechanical ventilator and were weaned from ventilator early compared to those who received Midazolam. They also experienced less tachycardia and hypertension. At the targeted sedation level, no difference was noted between the two groups of patients on mechanical ventilator support. In our study, we have compared the safety and efficacy of Dexmedetomidine versus Midazolam. And like the above research done by it was found that those patients who received Dexmedetomidine as a sedative were found to be weaned early from the ventilator and hence spent less time on mechanical ventilators.

However, as compared to Midazolam, bradycardia and hypotension were noted as side effects associated with Dexmedetomidine. The time required for extubation after cessation of Midazolam was with a mean value of 49.43 as compared to the patients who received Dexmedetomidine with a mean value of 27.76. P value was significant = 0.00001. Adams et al., (2013) carried out a different study evaluating the effectiveness of Midazolam and Dexmedetomidine needed for the sedation of patients admitted in intensive care units. For the critically ill patients in intensive care units, they conducted a systematic study comparing the sedative effects of Dexmedetomidine with Midazolam. Dexmedetomidine's superiority over Midazolam as a sedative often lacked clear evidence. The sedative effects of the two drugs were inconclusive in their study.

However, they discovered Dexmedetomidine to be a more cost-effective and secure substitute for Midazolam (Adams et al., 2013). This was in contrast to our study because Dexmedetomidine had more side effects, like hypotension and bradycardia. There was a statistically significant decrease in heart rate from the baseline from the first hour following the initiation of sedation till 2 hours after extubation. Also, there was more hypotension noted in group A patients than in group B patients. In our study, we found Dexmedetomidine to have an additional property of being an analgesic, thereby reducing the requirements of opioids and other analgesics. It was also found to have sympatholytic properties producing a decrease in heart rate and blood pressure. The patients who received Dexmedetomidine were weaned early from mechanical ventilators and thus spent less time intubated as compared to group B patients who were sedated with midazolam.

Dexmedetomidine was compared to Propofol or Midazolam required for sedation during mechanical ventilation in patients in a study by Jakob et al., (2012). The main intention of their study was to evaluate the effectiveness of Dexmedetomidine to Midazolam or Propofol in sustaining sedation, shortening the time the patient spent on mechanical ventilator machines and enhancing the patient's nursing care. They concluded that Dexmedetomidine was equally effective as Propofol and Midazolam at maintaining mild to moderate sedation. Dexmedetomidine also improved the patient's ability to verbalize discomfort compared to Propofol and Midazolam and decreased the time needed for mechanical ventilation compared to Midazolam. With Dexmedetomidine, they saw a higher incidence of adverse reactions. Their findings concurred with those of our study (Jakob et al., 2012).

Another study was conducted by Heybati et al., (2022) to observe the effectiveness of Dexmedetomidine in comparison to Propofol for sedation in patients requiring ventilator support. They conducted a systematic review and a randomized controlled trial. They concluded that Dexmedetomidine had no significant effect on the duration of the stay in the intensive care unit compared with Propofol but was found to have patients spending less time on mechanical ventilators, thereby reducing the risk of ICU related delirium. They also noted significant bradycardia in the patients who received Dexmedetomidine (Heybati et al., 2022).

The advantage of our study was to compare and determine the effectiveness of the two sedative agents used in critically ill patients requiring prolonged mechanical ventilation in a neurology critical care unit setup. It is very challenging to assess sedation levels in the already neurological impaired patients and provide necessary sedation breaks to evaluate the Glasgow coma scale of the patients. This study allowed us to determine sedation levels using the Richmond agitation sedation scale. Also, the study helped us to compare the time needed for extubation after the stoppage of two sedative drugs. The study's limitations include the exclusion of patients with severe liver damage, kidney failure requiring dialysis, those patients who got admitted following heart failure, and patients on neuromuscular blockade agents.

5. CONCLUSION

In evaluating two sedative drugs, it was found that Dexmedetomidine, when used as a sedative, resulted in early weaning from a mechanical ventilator compared to Midazolam in neurology intensive care unit patients. However, Dexmedetomidine was found to have more occurrence of bradycardia and hypotension when compared to Midazolam.

Ethical Approval

The study was approved by the Medical Ethics Committee of "Central Ethics Committee on Human Research" (CECHR). Ethical Approval CODE: DMIMS(D.U.)/I.E.C./8588.

Informed Consent

Written and oral informed consent was obtained from the relatives of all the individual participants included in the study.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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